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Debut of childhood acute lymphoblastic leukemia with malignant hypercalcemia, unusual presentation: a case report

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Abstract: Introduction. Leukaemia is the leading childhood cancer, with a 2022 incidence rate of 5.5 per 100,000 children. In the pediatric population, Hypercalcaemia maligna is one of its rare and severe paraneoplastic manifestations (overall incidence 0.4-1.3%). Objective. To present a case of acute lymphoblastic leukemia that debuted with severe hypercalcemia. Case description. It is about a 3-year-old female preschooler who started with a clinical picture characterized by bone pain and functional limitation; initial haemograms showed no alteration of cell lines, radiographs showed generalized osteopenia, accompanied by severe hypercalcemia, inhibited parathyroid hormone and secondary hypercalciuria, which were managed with intravenous hydration, diuretic, steroid and zoledronic acid. She also presented electrolyte imbalances that required potassium and phosphorus replacement with adequate response. Bone marrow studies were performed, confirming the diagnosis of acute lymphoblastic leukemia; she received ALLIC 2009 protocol chemotherapy with refractory disease at the end of the induction phase, and finally, a haploidentical bone marrow transplant, which was successful. Discussion. Hypercalcemia of malignancy is one of the endocrinological oncological emergencies with a low incidence, which is more frequent in the adult population. So, it is not the first diagnostic impression to be considered in pediatrics, leading to delays in aetiological diagnosis and prognosis. Conclusion. Hypercalcaemia accompanied by diffuse osteolytic lesions may be the first and only manifestation in the pediatric population with a diagnosis of acute lymphoblastic leukemia. Recognizing it will lead to the timely initiation of treatment, with an impact on survival.

Key words: hypercalcemia; case reports; precursor cell lymphoblastic leukemia-lymphoma; bone marrow; hematologic neoplasms

1 Introduction

Malignant hypercalcemia (MH) is defined as a marked elevation in serum calcium levels, which is secondary to the release of parathyroid hormone-related peptide (PTHrP) or 1.25 vitamin D, as well as to metastatic invasion of tumor cells into bone tissue [1]. This peptide shares the first 13 amino acids with parathyroid hormone (PTH), which is why it can act on the receptors of this hormone, stimulating bone resorption, phosphate excretion, and bone reabsorption in the renal tubules, thereby promoting hypercalcemia [2]. This manifestation is common in the adult population, occurring in

approximately 20–30% of cancer patients, with multiple myeloma being the cancer type with the highest incidence, ranging from 7.5% to 10.2% [1].

The symptoms associated with hypercalcemia have been described as nonspecific. It can range from a mild clinical presentation accompanied by vomiting, nausea, bone pain, and fever, to a more severe spectrum involving acidosis, coma, severe dehydration, renal failure, severe hypertension, and cardiac arrhythmias, requiring continuous monitoring, ideally in an intermediate or intensive care unit [3].

In the pediatric population, MH is primarily associated with solid tumors such as Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, and non-Hodgkin lymphoma. It is important to note that acute lymphoblastic leukemia (ALL) is the most common childhood cancer, accounting for approximately 28–30% of cases, with a peak incidence between 3 and 5 years of age, a scenario in which MH is considered a rare paraneoplastic manifestation, reported mainly in older age groups and without circulating blasts in peripheral blood, with an incidence of approximately 0.4–1.3% [4].

Studies have reported an association between the clinical manifestation of hypercalcemia in pediatric patients and genetic alterations such as the t (17;19) (q22;p13) translocation [5], as well as an association with the B phenotype and an initial white blood cell count < 20,000 [6]. However, there is no evidence demonstrating that it correlates with a worse prognosis or survival, as does the late diagnosis and initiation of chemotherapy, immunotherapy, or transplantation [7].

2 Case description

A 3-year-old female preschooler with no significant medical history presented with a 2-month-long clinical picture that her mother attributed to a minor trauma, characterized by progressive and limiting pain in the lower extremities. This required multiple visits to healthcare facilities, where no abnormalities were found, and outpatient management with analgesics and anti-inflammatory drugs was recommended. She was evaluated on an outpatient basis by the orthopedics department, which ordered a hip X-ray. However, due to marked limitation and limping, with an inability to walk, she presented to the emergency department of a tertiary-level pediatric clinic in Bucaramanga, Colombia. On admission, the physical examination revealed no lymphadenopathy or visceromegaly; range of motion in the major joints was preserved; deep palpation of the extremities showed no signs of pain or deformities; no inflammatory changes were documented; she was able to stand with irritability but with resistance to walking.

In the pediatric emergency department, initial laboratory tests were performed, revealing a complete blood count with no abnormalities in the cell lines, and X-rays of the hips, femur, and knees showed diffuse and heterogeneous osteopenia with multiple poorly defined radiolucent areas, an image suggestive of a pathological fracture in the distal metaphysis of the left femur; Thus, it is concluded that the radiological findings were consistent with myelopathy rather than Langerhans cell histiocytosis (LCH), which can be seen in Figures 1, 2, and 3 (belonging to the patient). In the multidisciplinary management, in conjunction with pediatric orthopedics, it was considered that the condition was due to a metabolic bone disease rather than a traumatic one; therefore, additional laboratory tests were performed, documenting severe hypercalcemia (16.8 mg/dL) and elevated uric acid (6.85 mg/dL), findings that were confirmed by the laboratory; Likewise, with the involvement of pediatric oncohematology, the team decided, in light of the severe hypercalcemia, to initiate treatment with hyperhydration calculated at 3,000 cc/m^2 /day, a (hydrocortisone) at a high dose of 10 mg/kg/day, and a loop diuretic (furosemide) calculated at 1 mg/kg per dose. She was transferred to the Pediatric Intermediate Care Unit for metabolic monitoring, where she required administration of zoledronic acid at a dose of 0.025 mg/kg, which gradually reduced her calcium levels to normal ranges.

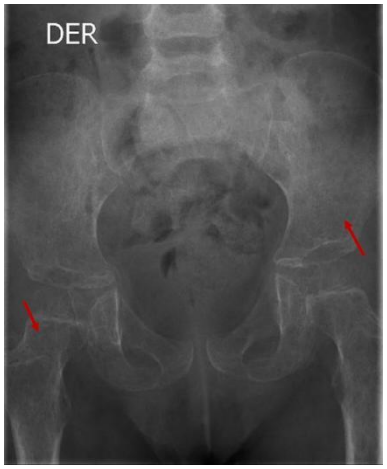

Figure 1. Anterior-posterior (AP) hip X-ray showing diffuse osteopenia with multiple poorly defined radiolucent areas diffusely distributed throughout the visualized bone structures. Source: prepared by the authors

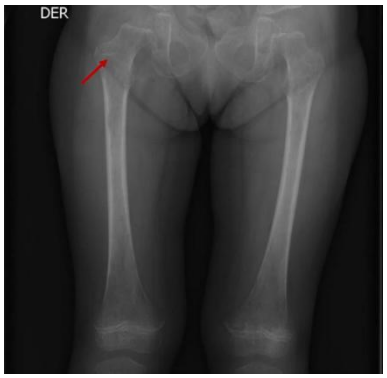

Figure 2. X-ray of long bones (femur), showing diffuse and heterogeneous changes in the visualized bone structures with patchy radiolucent areas predominantly in the metaphyses of the femurs. Source: prepared by the authors

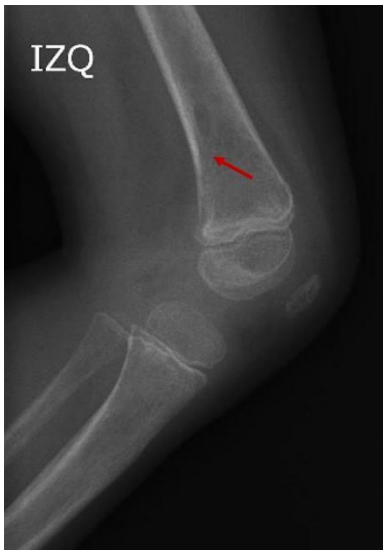

Figure 3. Lateral X-ray of the left knee showing cortical irregularity in the distal metaphysis of the left femur. Source: prepared by the authors

Within the management team, the pediatric endocrinologist's assessment was considered fundamental. Given the

patient's clinical and laboratory findings, the endocrinologist concluded that the hypercalcemia was due to suppressed PTH, noting the severe decline in calcium and phosphorus levels and their subsequent correction—a pattern suggestive of a "starving bone." Therefore recommended calcium and calcitriol supplementation, as well as continuing the search for a paraneoplastic or granulomatous disease. Consequently, she underwent a bone biopsy and bone marrow aspiration, which confirmed the diagnosis of B-cell precursor ALL through pathology results, warranting the initiation of chemotherapy with the ALLIC 2009 protocol. As she was refractory at the end of the induction phase, she was classified as having high-risk disease, which required a successful haploidentical bone marrow transplant, achieving remission of the cancer; she is currently more than 20 months relapse-free.

3 Discussion

ALL is a malignant proliferation of lymphoid cells, which remain at an early stage of differentiation and invade the bone marrow, blood, and extramedullary sites. It is considered the most common malignant disease in childhood, with a peak incidence between the ages of 2 and 5, and is more common in boys than in girls [5]. The Global Cancer Observatory (GLOBOCAN) estimated an age-adjusted incidence rate (IR) of childhood cancer for Colombia in 2022 of 14.0 new cases per 100,000 children, with leukemia being the most common type of cancer (age-adjusted IR of 5.5 per 100,000 children) [8]; according to the International Incidence of Childhood Cancer (IICC) for Colombia, the age-standardized IR ($x10^6$ person-years) from 2019 to 2020 was 40.2 and 8.2 for acute lymphoid and myeloid leukemia, respectively [9]. It is suspected based on the presence of characteristic clinical symptoms and signs, notably hepatomegaly, lymphadenopathy, muscle pain, fever, weight loss, and abnormalities in red blood cells, white blood cells, and platelets.

Treatment is based on globally established protocols that consist of defined phases, from induction to maintenance, along with prophylactic or therapeutic therapy for leukemic infiltration of the central nervous system (CNS), which has shown a steady improvement in survival rates among children and adolescents with this disease [10,11].

In recent years, a decline in the mortality rate has been achieved, with a high survival rate exceeding 65% in developing countries and over 80% in developed countries for childhood ALL. This is based on advances in chemotherapy and immunotherapy regimens, where many other (molecular and environmental) have set the standard for a favorable or unfavorable response to treatment [12].

Within its broad spectrum of clinical manifestations at onset, malignant hypercalcemia (MH) represents the most common endocrinological oncological emergency, but with a very low overall incidence of 0.4–1.3% in the pediatric population [6]. The few cases reported in the literature are described in association with solid tumors and, on rare occasions, with ALL or chronic myeloid leukemia (CML).

The complete blood count in most of these patients is normal, with atypical or nonspecific findings, similar to what was observed in our patient's case, where symptoms of bone and muscle pain and difficulty walking were more prominent. Hypercalcemia in this scenario is explained by the infiltration and destruction of the bone marrow by leukemic cells, involving the secretion of humoral factors such as PTHrP, tumor necrosis factor (TNF) alpha and beta, transforming growth factor beta, interleukins 1 and 6, as well as vitamin D [3], which was accompanied by suppressed parathyroid hormone and secondary hypercalciuria.

The primary goal in evaluating hypercalcemia caused by malignant neoplasms is to direct management toward reducing serum calcium levels and treating the underlying disease. Principles for reducing calcium levels include hyperhydration, forcing diuresis with diuretics, and the combination of calcitonin and bisphosphonates— which have the potential to lower levels more rapidly—while seeking to avoid rebound hypocalcemia; the use of zoledronic acid has become increasingly prominent. Only in cases where there is no response to pharmacological therapy and the patient's

clinical condition becomes critical should temporary dialysis be considered [3]. In this case, the patient responded positively to the treatment regimen, including IV steroids, without the use of calcitonin or bisphosphonates, achieving a semi-automated decrease in calcium from 16.8 mg/dL to 9.4 mg/dL by the fifth day of treatment.

The most recent study published on malignant hypercalcemia in Colombia was in 2022, but it focused on the adult population. It concluded that further studies are still needed to gain a better understanding of the factors related to its presentation, particularly regarding cases reported in the pediatric population, which are much rarer [13].

The recommendation is to pay closer attention to the persistence of symptoms and their progression over time, especially in cases where there is no evidence of improvement and all test results appear to be within normal limits; likely, having conducted a more comprehensive search at an earlier and more timely stage would have led to an earlier investigation of lymphoproliferative disease, which would have confirmed the correct diagnosis and even prevented the onset of pathological fractures and their associated complications.

In the management of cancer patients, it is essential to emphasize the importance of teamwork, especially when the treating team faces complex clinical situations, where perspectives from different disciplines help guide and establish a better diagnosis. In the case in question, the interdisciplinary team composed of specialists in pediatrics, pediatric oncohematology, pediatric endocrinology, and pediatric orthopedics was essential. Equally important was the support provided to both the patient and their family by the team of comprehensive therapists, social workers, and psychologists, who, understanding how cancer affects every aspect of an individual and their family, accompanied them and helped foster a better understanding of the diagnosis and the disease, as well as the treatment and recovery process, thereby helping to strengthen support networks, given that in this case it involved a blended family with separated parents.

All of the above highlights the importance of bringing our patient's case to the attention of the scientific community, as it presents an uncommon presentation that could be confused with other pathologies, bearing in mind the diversity of clinical presentations it may involve—a scenario that still faces many barriers, which we must continue tirelessly to overcome.

4 Conclusion

Hypercalcemia, either on its own or in combination with osteolytic lesions, may be the primary clinical manifestation at the onset of ALL in the pediatric population. Although rare, we must remain vigilant for this presentation, especially in the very early stages of the disease, when even the complete blood count may appear normal, leading to misdiagnoses or delayed diagnoses that impact patient prognosis and survival.

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Ethical consideration

It is hereby declared that no experiments were conducted on humans or animals for this publication. Furthermore, the protocols stipulated for the publication of patient data were followed; this was done with prior authorization and the informed consent of the responsible caregiver, thereby ensuring the privacy and confidentiality of the patient's identity and the proper handling of personal data. The study was conducted and published with the approval of the institution's ethics committee.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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